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PATENT

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Gary R. Fabian	Gary R Fabian	23 Feb 2008
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE	
In Re Application of: Williams, A., et al.	Confirmation No. 6889
Serial No.: 09/410,462	Art Unit: 1635
Filing Date: 1 October 1999	Examiner: J.E. Angell
Title: A SINGLE AGENT METHOD FOR KILLING TUMOR AND TUMOR ASSOCIATED ENDOTHELIAL CELLS USING ADENOVIRAL MUTANTS	

BRIEF ON APPEAL

Mail Stop: Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This is an appeal of the Office Action mailed on 27 March 2007, finally rejecting claims 6, 7, 11-13, 15, 17, 18 and 29. An Amendment and Response to Final Office Action and Notice of Appeal was filed by appellants on 27 September 2007. An Advisory Action was mailed on 25 October 2007. Accordingly, the Appeal Brief was due, without extension, on 27 November 2007. A Request for Three-Month Extension of Time accompanies this brief in the transmittal. Thus, the due date with three-month extension is 27 February 2008. Authorization to charge the deposit account for the fee required under 37 CFR 41.20(b)(2) for filing an appeal brief accompanies this brief in the transmittal.

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PERSONAL APPEARANCE BEFORE THE BOARD OF APPEALS IS WAIVED

Appellants waive the opportunity for a personal appearance before the Board of Appeals to argue the issues of this appeal.

REAL PARTY IN INTEREST

The real party in interest in the present application is ONYX PHARMACEUTICALS, INC. The assignment of rights by the applicants of this application to Onyx Pharmaceuticals, Inc., is of record in the present application. The Reel/Frame numbers for the recorded assignment is as follows: 010405/0417.

RELATED APPEALS AND INTERFERENCES

Appellants are unaware of any prior or pending related appeals, interferences or judicial proceedings.

STATUS OF CLAIMS

Claims 6-11, 15, 17-20, 26-28, and 34 are pending (based on the Advisory Action, dated 25 October 2007). Claims 26-28 are allowed. Claims 8-10, 19, 20, and 34 are objected to. Claims 6, 7, 11, 15, 17, and 18 are rejected. Claims 1-5, 12-14, 16, 21-25, and 29-33 are canceled.

The rejection of claims 6, 7, 11, 15, 17, and 18 is appealed herein.

STATUS OF AMENDMENTS

The status of amendments filed subsequent to final rejection are as follows: appellants' amendments to the claims and arguments, presented in appellants' Amendment and Response to Final Office Action, dated 27 September 2007, are of record for the purposes of appeal.

In the Advisory Action, dated 25 October 2007, the Examiner states on the first page that the amendments to the claims in appellants' response dated 27 September 2007, "will be entered" for the purposes of appeal. The Examiner indicated withdrawal of the following rejections (*see* Advisory Action, continuation sheet, continuation of 5):

Claim 22 under 35 U.S.C. §102(b) asserting that the claim is anticipated by Whyte, et al. (J. Virol. 1988);

Claim 23 under 35 U.S.C. §102(b) asserting that the claim is anticipated by Jelsma, et al. (Virol. 1989); and

Claims 6-13, 15, 17-20, and 29-34 under 35 U.S.C. §112, first paragraph, asserting a scope of enablement rejection.

The Examiner states that "[a]pplicants arguments against the rejection of claims 6, 7, 11, 15, 17 and 18 under 35 U.S.C. 102(e) have been fully considered but are not persuasive" (*see* Advisory Action, continuation sheet, continuation of 13).

Further, the Examiner notes the following: "claims 8-10, 19, 20 and 34 are objected to, but if the base claims (claims 11 and 15) were re-written to include the limitation of these claims, all claims would be allowed. That is, limiting claims 11 and 15 such that the adenovirus was d1922/947, dli107 or pm928 would obviate the rejections." *See* Advisory Action, continuation sheet, continuation of 13, last sentence.

SUMMARY OF THE CLAIMED SUBJECT MATTER

There are three groups of claims pending in the present application. The first group of claims contains independent claims 26-28. The second group of claims relates to independent claim 11 and its dependent claims. The third group of claims relates to independent claim 15 and its dependent claims. The claims of the first group are allowed and not under appeal. The claims of the first group relate to compositions comprising a Rb binding site adenoviral mutant with a negative selection agent operably linked to a promoter, wherein the mutant is dl922/947, dl1107, or pm928. Claims 11, 6, 7 and 15, 17, and 18 of the second and third groups, respectively, are under appeal and generally relate to methods of killing dividing endothelial cells (*e.g.*, microvascular endothelial cells) with substantially less killing of quiescent endothelial cells using a replication competent adenovirus comprising a mutation in an E1A CR2 RB family member binding region.

In the first group of claims, corresponding to independent claims 26-28, the claims are directed to a composition comprising a Rb binding site adenoviral mutant with a negative selection agent operably linked to a promoter, wherein the mutant is dl922/947, dl1107, or pm928 (*see, e.g.,* specification page 4, lines 4-6; page 6, line 31, to page 7, line 1; page 7, line 15, to page 8, line 15; page 10, lines 4-16; pages 13-14; Examples, pages 16-20; and original claims 21-28).

In the second group of claims, the claims are directed to a method for killing dividing endothelial cells with substantially less killing of the quiescent endothelial cells (independent claim 11; *see, e.g.*, specification, Abstract; page 9, line 22, to page 10, line 2; page 12, lines 10-15; original claim 11). The method comprising contacting a cell population, comprising dividing and quiescent endothelial cells, under infective conditions with a replication competent adenovirus (*see, e.g.*, specification, page 9, line 22, to page 10, line 2; page 6, lines 11-19; original claim 11). The adenovirus comprises a mutation in an E1A CR2 RB family member binding region of the adenovirus (*see, e.g.*, specification FIG. 1; page 4, lines 4-6; original claim 11). A sufficient time for the mutant adenovirus to infect the cell population is allowed (*see, e.g.*, specification page 9, line 9, to page 10, line 2; original claim 11). The mutant adenovirus replicates to higher titers in the dividing cells than wild type adenovirus (*see, e.g.*, specification Abstract; Example 2, pages 17-18; original claim 11). The

contacting is by direct administration of the replication competent adenovirus to the cell population (*see, e.g.*, specification pages 13-14; and Examples 3 and 4, pages 18-20).

The mutation in the E1A-CR2 region may, in an adenovirus type 5, comprise a deletion or substitution of one or more amino acids 122 through 129 encoded by the E1A-CR2 region (*see* pending claim 6). Alternatively, the mutation in the E1A-CR2 region may, in an adenovirus type 5, comprise a deletion or substitution of one or more amino acids 111 through 123 (*see* pending claim 7). Specific embodiments of adenoviruses comprising mutations in the E1A-CR2 region include dl922/947 (*see* pending claim 8), dl1107 (*see* pending claim 9), and pm928 (*see* pending claim 10).

In the third group of claims, the claims are directed to a method for controlling angiogenesis in an animal by substantially and selectively killing dividing microvascular endothelial cells compared to quiescent microvascular endothelial cells (independent claim 15; *see, e.g.*, specification Abstract; page 3, lines 8-11; page 6, lines 27-30; page 9, line 22, to page 10, line 2; page 12, lines 10-32; original claim 15). The method comprises administering to the animal in need of the control a replication competent adenovirus comprising a mutation in an E1A-CR2 RB family member binding region of the adenovirus (*see, e.g.*, specification FIG. 1; page 4, lines 4-6; page 9, line 22, to page 10, line 2; page 6, lines 11-19; original claim 15). A sufficient time for the mutant adenovirus to infect the microvascular endothelial cells is allowed (*see, e.g.*, specification page 9, line 9, to page 10, line 2; original claim 15). The administering is by direct administration of the replication competent adenovirus to the microvascular endothelial cells (*see, e.g.*, specification pages 13-14; and Examples 3 and 4, pages 18-20).

The mutation in the E1A-CR2 region may, in an adenovirus type 5, comprise a deletion or substitution of one or more amino acids 122 through 129 encoded by the E1A-CR2 region (*see* pending claim 17). Alternatively, the mutation in the E1A-CR2 region may, in an adenovirus type 5, comprise a deletion or substitution of one or more amino acids 111 through 123 (*see* pending claim 18). Specific embodiments of adenoviruses comprising mutations in the E1A-CR2 region include dl922/947 (*see* pending claim 19), dl1107 (*see* pending claim 20), and pm928 (*see* pending claim 34).

The rejection of independent claims 11 and 15, as well as dependent claims 6, 7, 17 and 18 are the subject of this appeal.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Sole Issue

In the final Office action, dated 27 March 2007, and the Advisory Action, dated 25 October 2007, the Examiner rejected claims 6, 7, 11, 15, 17, and 18 under 35 U.S.C. §102(e) asserting that the claims are anticipated by Bischoff, et al., U.S. Patent No. 6,080,578 (*see* Advisory Action, dated 25 October 2007, continuation page, continuation of 13).

ARGUMENT

1.0.0 Sole Issue

In the final Office action, dated 27 March 2007, and the Advisory Action, dated 25 October 2007, the Examiner rejected claims 6, 7, 11, 15, 17, and 18 under 35 U.S.C. §102(e) asserting that the claims are anticipated by Bischoff, et al., U.S. Patent No. 6,080,578 (*see* Advisory Action, dated 25 October 2007, continuation page, continuation of 13).

1.1.0 The Examiner has failed to establish anticipation of the presently claimed invention.

In the present application, independent claims 11 and 15 are pending. Following herein below, the appellants set forth their arguments that the cited reference does not anticipate the claimed invention at least with respect to the limitations present in the independent claims. Accordingly, the dependent claims define over the cited prior art at least by virtue of their inclusion of the limitations of the independent claims.

Appellants submit that the reference of Bischoff, et al., does not anticipate the claimed invention for reasons of record as previously discussed by appellants; specifically, (1) the reference of Bischoff, et al, does not teach all of the elements of the present invention; and (2) the Examiner has failed to establish a *prima facie* case of inherency as the reference of Bischoff, et al, does not inherently teach all of the elements of the present invention.

Finally, appellants briefly discuss how the fact pattern of the present case distinguishes it from the fact patterns of the case law cited by the Examiner.

1.1.1 The reference of Bischoff, et al, does not expressly teach all of the elements of the present invention.

Federal Circuit decisions repeatedly emphasize that anticipation can be established only if all the elements of a claimed invention are identically set forth in a single prior art reference. The test is strict, not substantial, identity. *See, e.g., Transclean Corp. v. Bridgewood Services, Inc.*, 290 F.3d 1364, 62 USPQ2d 1865 (Fed. Cir. 2002); *Sandt Technology, Ltd. V. Resco Metal and Plastics Corp.*, 264 F.3d 1344, 60 USPQ2d 1091 (Fed. Cir. 2001); *EMI Group North America Inc. v. Cypress Semiconductor Corp.*, 268 F.3d 1342, 1350, 60 USPQ2d 1423 (Fed. Cir. 2001) ("A prior art reference anticipates a patent claim if

the reference discloses, either expressly or inherently, all of the limitations of the claim").

Both of the pending independent method claims (i.e., claims 11 and 15) comprise two limitations not taught by the reference of Bischoff, et al., (i) a limitation relating to preferential killing of dividing endothelial cells compared to quiescent endothelial cells, and (ii) a limitation that the claimed method is carried out by direct administration of a replication competent adenovirus, comprising a mutation in an E1A CR2 RB family member binding region, to endothelial cells. Further, claim 11 contains the limitation that the mutant adenovirus (i.e., a replication competent adenovirus comprising a mutation in an E1A CR2 RB family member binding region) versus wild-type adenovirus replicates to higher titers in the dividing endothelial cells, and claim 15 contains the limitation of "controlling angiogenesis in an animal." The reference of Bischoff, et al., does not teach either of these limitations. Claims 11 and 15 are as follows:

> 11. In a cell population comprising dividing and quiescent endothelial cells, a method for killing said dividing endothelial cells with substantially less killing of said quiescent endothelial cells, said method comprising contacting said cell population under infective conditions with a replication competent adenovirus, said adenovirus comprising a mutation in an E1A CR2 RB family member binding region of said adenovirus, and allowing sufficient time for said mutant adenovirus to infect said cell population, wherein said mutant adenovirus replicates to higher titers in said dividing cells than wild type adenovirus and said contacting is by direct administration of the replication competent adenovirus to the cell population.
>
> 15. A method for controlling angiogenesis in an animal by substantially and selectively killing dividing microvascular endothelial cells compared to quiescent microvascular endothelial cells, said method comprising administering to said animal in need of said control a replication competent adenovirus comprising a mutation in an E1A-CR2 RB family member binding region of said adenovirus, and allowing sufficient time for said mutant adenovirus to infect said microvascular endothelial cells, wherein said administering is by direct administration of the replication competent adenovirus to the microvascular endothelial cells.

The teachings of the reference of Bischoff, et al., relate to "methods and compositions for **ablating neoplastic cells by infecting the neoplastic cells** with a recombinant adenovirus which is substantially replication deficient in non-neoplastic cells and which exhibits at least a partial replication phenotype in neoplastic cells" (*see* Bischoff, et al., col. 3, lines 8-13; emphasis added). The reference of Bischoff, et al., teaches "(t)he mutant virus is

able to substantially produce a replication phenotype in **neoplastic cells** but is substantially unable to produce a replication phenotype in non-replicating, non-neoplastic cells having essentially normal p53 and/or RB function" (*see* Abstract of Bischoff, et al.; emphasis added).

The reference of Bischoff, et al., does not teach that replication competent adenovirus, comprising a mutation in an E1A CR2 RB family member binding region, demonstrates enhanced replication in and killing of dividing endothelial cells (*e.g.*, microvascular endothelial cells) versus quiescent endothelial cells. *See, e.g.*, appellants' Amendment and Response, dated 27 September 2007, pages 4-5. In the final Office action, the Examiner concurs that the reference of Bischoff, et al., does not teach all of the elements of the presently claimed invention:

> Although Bischoff et al. is silent with respect to the limitations in the instant claims that the method would result in selective killing of dividing endothelial cells relative to killing of quiescent endothelial cells, Bischoff et al. anticipates all of the claimed active method steps, so the function effects of the claimed methods are considered to be inherent in the method steps taught by Bischoff, et al. (Emphasis added; final Office action, mailed 27 March 2007, page 11).

Also, the reference does not teach direct administration of a mutant adenovirus to endothelial cells. Further, the reference of Bischoff, et al., provides no teaching concerning mutant adenovirus replicating to higher titers in the dividing endothelial cells than wild type adenovirus as is set forth as a limitation in claim 11 (*see* appellants' Amendment and Response, dated 27 September 2007, page 4). Finally, the reference of Bischoff, et al., does not teach control of angiogenesis in an animal as a method of controlling neoplastic cell growth.

Accordingly, appellants submit that the reference of Bischoff, et al., does not teach all of the elements of the claimed invention. Therefore, in order to assert that the reference anticipates the presently claimed invention, the Examiner must establish that the reference inherently teaches all of the claimed elements of the methods of the present invention.

1.1.2 The Examiner has failed to establish a *prima facie* case of inherency.

First, inherency is not present when prior art is only capable of being modified. To establish inherency, the extrinsic evidence "must make clear that the missing descriptive

matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *See Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991); emphasis added. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. *See Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1269, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991) (quoting *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (C.C.P.A. 1981)). The fact that a prior art reference is capable of being modified and the resulting modification would anticipate the invention is not sufficient to support anticipation based on inherency. In *In re Robertson* (169 F.3d 743, 749 USPQ2d 1949 (Fed. Cir. 1999)), the Federal Circuit reversed an anticipation holding because the prior art was only capable of being modified and one of ordinary skill would not have recognized such modification.

Appellants discussed the reference of Bischoff, et al., and modifications proposed by the Examiner, for example, in their Amendment and Response to Final Office action, dated 27 September 2007, pages 5-6.

In the present application, a method of killing dividing endothelial cells with substantially less killing of quiescent cells by contacting the cells under infective conditions with a mutant adenovirus is not inherent in the teachings of Bischoff, et al., for the following reasons. Not all tumors comprise neoplastic cells that are $RB^{(-)}$ (*see* Bischoff, et al., col. 7, lines 47-63; col. 9, lines 20-55). The reference of Bischoff, et al., teaches method of ablating tumor cells by administration of a mutant adenovirus comprising a mutation in the E1A CR2 domain to:

> A cell population (such as a mixed cell culture or a human cancer patient) which comprises a subpopulation of neoplastic cells lacking RB function and a subpopulation of non-neoplastic cells which express essentially normal RB function can be contacted under infective conditions (i.e., conditions suitable for adenoviral infection of the cell population, typically physiological conditions) with a composition comprising an infectious dosage of a E1a - $RB^{(-)}$ replication deficient adenovirus. Such contacting results in infection of the cell population with the E1a -$RB^{(-)}$ replication deficient adenovirus. The infection produces preferential expression of a replication phenotype in a significant fraction of the cells comprising the subpopulation of neoplastic cells lacking RB function but does not produce a substantial expression of a replicative phenotype in the subpopulation of non-neoplastic cells having essentially normal RB function. The expression of a replication phenotype in

> an infected $RB^{(-)}$ cell results in the death of the cell, such as by cytopathic effect (CPE), cell lysis, apoptosis, and the like, resulting in a selective ablation of neoplastic $RB^{(-)}$ cells from the cell population. (Bischoff, et al., col. 9, line 56, to col. 10, line 9; emphasis added.)

The Examiner asserts that one of ordinary skill in the art knows "that patients comprising tumors comprise both dividing cells, such as proliferating cancer cells and proliferating microvascular endothelial cells associated with the tumor" (Final Office action, mailed 27 March 2007, pages 3-4). However, the reference of Bischoff, et al., only teaches the use of E1A-$RB^{(-)}$ replication defective adenovirus mutants in methods of ablating $RB^{(-)}$ neoplastic cells. It is not inherent in the method taught by Bischoff, et al., to infect endothelial cells with E1A-$RB^{(-)}$ replication defective adenovirus mutants regardless of the RB-expression status of the neoplastic cells. The presently claimed invention is directed to methods of killing endothelial cells independent of the RB-expression status of the neoplastic cells. Accordingly, even in the situation where a tumor does not display loss of RB gene function, the method of the present invention is effective to kill dividing endothelial cells within the tumor.

Following the teachings of the reference of Bischoff, et al., there is no reason that one of ordinary skill in the art would administer an adenovirus comprising a mutation in an E1A CR2 RB family member binding region to a tumor cell population that did not comprise $RB^{(-)}$ cells. However, following the methods of the claimed invention one of ordinary skill is directed to treat populations of cells comprising tumor cells and dividing endothelial cells with an adenovirus comprising a mutation in an E1A CR2 RB family member binding region regardless of the RB-expression status of the target tumor.

Accordingly, the mere fact that a one of ordinary skill in the art may administer an adenovirus comprising a mutation in an E1A CR2 RB family member binding region to a tumor cell population comprising $RB^{(-)}$ cells does not make it certain that one of ordinary skill in the art would do the same for any tumor cell populations (*e.g.*, when the tumor cell population is not $RB^{(-)}$). As noted above, inherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. *See Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1269, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991) (quoting *In re Oelrich*, 666 F.2d 578,

581, 212 USPQ 323, 326 (C.C.P.A. 1981)).

Further, in regard to claim 11, there is no reason for one of ordinary skill in the art to conclude from the teachings of the reference of Bischoff, et al., that administration of the mutant adenovirus to dividing endothelial cells results in the mutant adenovirus replicating to higher titers in the dividing cells than wild type adenovirus regardless of the RB-expression status of associated tumor cells. Also, in regard to claim 15, there is no reason for one of ordinary skill in the art to conclude from the teachings of the reference of Bischoff, et al., that direct administration of the replication competent adenovirus to dividing microvascular endothelial cells would provide a method for controlling angiogenesis in an animal regardless of the RB-expression status of the tumor cells.

Accordingly, even if, *in arguendo,* the reference of Bischoff, et al., is capable of being modified to achieve the method of the present invention, the Examiner has not presented any evidence that makes it clear that the missing descriptive matter described herein above is necessarily present in the cited reference.

Second, "[a] reference includes an inherent characteristic if that characteristic is the 'natural result' flowing from the reference's explicitly explicated limitations." *See Eli Lilly & Co. v. Barr Laboratories, Inc.,* 251 F.3d 955, 970, 58 USPQ2d 1865 (Fed. Cir. 2001). In the present case, the claimed invention is not a natural result flowing from the disclosure of the Bischoff, et al., as previously discussed by appellants (*see* appellants' Amendment and Response, dated 27 September 2007, pages 8-9) and as discussed herein below.

The reference of Bischoff, et al., lacks descriptive matter related to killing of dividing endothelial cells by direct administration of a mutant adenovirus. To support the rejection, the Examiner asserts the following:

> It is noted that patients comprising tumors comprise both dividing cells, such as proliferating cancer cells and proliferating microvascular endothelial cells associated with the tumor, as well as non-dividing non-cancerous cells. Therefore, Bischoff teaches administering an mutant adenovirus directly to tumor wherein the mutant adenovirus meets all of the structural limitations of the rejected claims. Therefore, administering the mutant adenovirus taught by Bischoff to a tumor would necessarily result in substantially and selectively killing dividing endothelial cells (including dividing microvasculature) and cancer cells in the subject. (Advisory Action, continuation page, continuation of 13.)

In the absence of the teachings of the present specification, one of ordinary skill in the art would not be guided to use replication competent adenovirus to preferentially kill dividing endothelial cells relative to killing of quiescent endothelial cells, which in and of itself provides an art recognized cancer treatment (i.e., disruption of tumor angiogenesis) distinct from direct killing of tumor cells (i.e., neoplastic cells).

The claimed methods of the present invention relate to direct administration of mutant adenovirus to dividing endothelial cells to provide preferential killing of dividing endothelial cells relative to killing of quiescent endothelial cells, notably microvascular endothelial cells, by the mutant adenovirus. The endothelium comprises a single layer of flat cells that line the interior surface of blood vessels. The endothelium forms an interface between circulating blood in the lumen and the rest of the vessel wall. Endothelial cells are the cells that make up the inside of blood vessels. Angiogenesis is the formation of new blood vessels. Angiogenesis has come to be appreciated as a continuous and important process in tumor development, wherein a tumor may gain an independent blood supply. The process of angiogenesis is believed to be driven by the tumor releasing signals that induce angiogenesis, such as VEGF, by binding to endothelial cell receptors near the tumor (*see, e.g.*, Berse, B., et al., Molec. Cell. Biol. 1992 Feb;3(2):211-20); Warren, R.S., et al., J. Clin. Invest. 1995 Apr;95(4):1789-97). The control of tumor angiogensis is generally seen to be an alternative method of controlling tumor growth versus direct destruction of tumor cells (*see, e.g.*, Berse, et al., paragraph bridging pages 218-219; Warren, et al., paragraph bridging cols. 1-2, page 1789). Accordingly, the claimed invention is not a natural result flowing from the disclosure of the Bischoff, et al., reference because the reference teaches "methods and compositions for **ablating neoplastic cells by infecting the neoplastic cells** with a recombinant adenovirus which is substantially replication deficient in non-neoplastic cells and which exhibits at least a partial replication phenotype in neoplastic cells" (*see* Bischoff, et al., col. 3, lines 8-13; emphasis added)..

The reference of Bischoff, et al., contains no explicitly explicated limitations from which the 'natural result' flowing from the reference's teachings would result in the use of the described adenoviral vectors as an alternative method of controlling tumor growth, that is, direct administration of mutant adenovirus to endothelial cells for preferential killing of dividing endothelial cells relative to killing of quiescent endothelial cells, notably

microvascular endothelial cells. The reference of Bischoff, et al., teaches only the killing of $RB^{(-)}$ tumor cells by administration of replication competent adenovirus comprising a mutation in an E1A CR2 RB family member binding region to the $RB^{(-)}$ tumor cells.

There is no teaching in the reference of Bischoff, et al., that would guide one of ordinary skill in the art to use the methods of the present invention to achieve a method for preferential killing of dividing endothelial cells relative to killing of quiescent endothelial cells. For example, in a situation where a target tumor (regardless of RB-expression status of the tumor cells) did not respond to direct killing of neoplastic cells by a selected method (*e.g.*, chemotherapy), in view of the teachings of the present specification one of ordinary skill in the art may choose to administer a mutant adenovirus to the dividing endothelial cells to reduce or eliminate angiogenesis which provides a blood supply to a tumor. The teachings of Bischoff, et al., would not direct one of ordinary skill in the art to such an approach. Inherency must flow as a necessary conclusion from the prior art, not simply a possible one. *See, e.g., In re Oelrich,* 666 F.2d 578, 581, 212 USPQ 323, 326 (C.C.P.A. 1981). Accordingly, the teachings of the reference of Bischoff, et al., do not inherently anticipate the claimed invention.

Third, the Federal Circuit has cautioned that all claimed elements must be found in the prior art for anticipation to be found:

> For a prior art reference to anticipate a claim, the reference must disclose each and every element of the claim with sufficient clarity to prove its existence in the prior art .... Although this disclosure requirement presupposes the knowledge of one skilled in the art of the claimed invention, that presumed knowledge does not grant a license to read into the prior art reference teachings that are not there. *Motorola, Inc. v. Interdigital Tech. Corp.*, 121 F.3d 1461, 1473, 43 USPQ2d 1481, 1490 (Fed. Cir. 1997).

In the present case, the Examiner has presupposed the knowledge of one skilled in the art (i.e., "patients comprising tumors comprise both dividing cells, such as proliferating cancer cells and proliferating microvascular endothelial cells associated with the tumor," Final Office action, mailed 27 March 2007, pages 3-4); however, that presumed knowledge does NOT grant the Examiner a license to read into the reference of Bischoff, et al., teachings that are not there (*e.g.*, a method of killing dividing endothelial cells with substantially less killing of quiescent cells by direct administration of a mutant adenovirus to

the cells under infective conditions). *See* appellants' Amendment and Response, dated 27 September 2007, pages 6-7.

Further, the presupposed knowledge applied by the Examiner does not prove the existence in the cited prior art of a method of administering a replication competent adenovirus comprising a mutation in an E1A CR2 RB family member binding region to tumor cells regardless of RB-expression status. The reference of Bischoff, et al., does not teach or suggest any such method.

In view of the above-presented arguments, appellants submit that the Examiner has failed to establish a case of anticipation for the claimed invention. Further, the Examiner has failed to establish a *prima facie* case of inherency.

1.1.3 Brief discussion of the case law cited by the Examiner.

In the Advisory Action, dated 25 October 2007, the Examiner recites four cases to support the asserted inherency rejection. Following herein, appellants summarize important distinctions between the fact patterns of the cases recited by the Examiner and the present application.

First, regarding *In re Best* the Examiner asserts the following:

> Applicant is reminded that MPEP § 2112.01 indicates, "Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). 'When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." Applicant is also reminded that MPEP § 2112 indicates, "[T]he claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPO 430,433 (CCPA 1977)." (Advisory Action, dated 25 October 2007, continuation page, continuation of 13.)

The holding regarding inherency in *In re Best* was discussed by the CCPA as follows:

> All the positive process limitations are expressly disclosed except for the functionally expressed rate of cooling. However, there is nothing to indicate that this rate of cooling in any way differs from the normal rate resulting from removal of the heat source. Thus, the examiner's conclusion that those parameters of the resultant product which are recited in the appealed claims but are not expressly disclosed in the reference would be inherent is a reasonable one, absent convincing evidence to the contrary. (*In re Best*, 562

F.2d 1252, 1254, 195 USPO 430, 433 (CCPA 1977); emphasis added.)

In the present case the prior art method is not substantially identical to the presently claimed method. First, the presently claimed "positive process limitations" are not disclosed by the reference of Bischoff, et al. The reference teaches "methods and compositions for **ablating neoplastic cells by infecting the neoplastic cells with a recombinant adenovirus** which is substantially replication deficient in non-neoplastic cells and which exhibits at least a partial replication phenotype in neoplastic cells" (*see* Bischoff, et al., col. 3, lines 8-13; emphasis added). The present invention claims preferential killing of dividing endothelial cells compared to quiescent endothelial cells carried out by direct administration of a mutant adenovirus to endothelial cells. Second, the method of the present invention does in fact differ from the method taught by the reference of Bischoff, et al. For the reasons discussed herein above, the method of direct ablation of neoplastic cells comprising administration of a mutant adenovirus to the neoplastic cells taught by the reference is different from the presently a method of killing dividing endothelial cells by direct administration of mutant adenovirus; specifically, these methods relate to different approaches for the treatment of tumors (direct ablation of tumor cells versus targeting angiogenesis, respectively), wherein the methods of the present invention, unlike the teachings of the reference, are not limited to tumor cells that have lost RB gene function.

Accordingly, appellants submit that the Examiner has failed to establish anticipation based on inherency and further evidence from appellants is therefore not required.

Second, regarding *Schering Corp. v. Geneva Pharm. Inc.*, the Examiner asserts the following:

> There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. Schering Corp. v. Geneva Pharm. Inc., 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003). (Advisory Action, dated 25 October 2007, continuation page, continuation of 13.)

The holding regarding inherency in *Schering Corp. v. Geneva Pharm. Inc.* was discussed by the Federal Circuit as follows:

> Other precedents of this court have held that inherent anticipation does not require that a person of ordinary skill in the art at the time would have recognized the inherent disclosure. *E.g., In re Cruciferous Sprout Litig., 301 F.3d 1343, 1351 (Fed. Cir. 2002)*; *Mehl/Biophile Int'l Corp. v. Milgraum,*

> *192 F.3d 1362, 1366 (Fed. Cir. 1999)* ("Where . . . the result is a necessary consequence of what was deliberately intended, it is of no import that the article's authors did not appreciate the results."). *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003); emphasis added.

As discussed herein above, the result of the method of the present invention is not a necessary consequence of what was deliberately intended by the teachings of the reference of Bischoff, et al.. This is certainly the case in view of the fact that the reference only teaches administration of E1A-RB$^{(-)}$ adenovirus mutants for ablation of tumor cells that have lost RB gene function. As discussed herein above, there is no inherent disclosure of the method of the present invention in the reference of Bischoff, et al.

Third, regarding *Ex parte Novitski*, the Examiner asserts the following:

> It is also noted that Ex parte Novitski, 26 USPQ2d 1389 (Bd. Pat. App. & Inter. 1993), indicates that a reference teaching a claimed process, wherein one of the claimed properties of a product used in the prior art process is inherent but undisclosed by the reference, may be properly applied as art against the claimed process. (Advisory Action, dated 25 October 2007, continuation page, continuation of 13.)

In Ex parte Novitski the method claim under consideration had the identical positive process limitation as the cited reference (i.e., "comprises the step of inoculating said plant with a nematode-inhibiting strain of P. cepacia which strain colonizes the plant"). In the present case, the method claims under consideration do not have an identical positive process limitation because the present method claims require direct administration of mutant adenovirus to endothelial cells and the reference of Bischoff, et al., teaches administration of mutant adenovirus to tumor cells that have lost RB gene function.

Finally, regarding *Integra Life Sciences I Ltd. v. Merck KGaA*, the Examiner asserts the following:

> Furthermore, Integra Life Sciences I Ltd. v. Merck KGaA, 50 USPQ2d 1846 (DC SCalif, 1999) indicates that a reference teaching a process may anticipate claims drawn to a method comprising the same process steps, despite the recitation of a different intended use in the preamble or the later discovery of a particular property of one of the starting materials or end products.

The holding regarding inherency in *Integra Life Sciences I Ltd. v. Merck KGaA* was discussed by the U.S. District Court as follows:

> The court will not and need not address whether the alleged preamble

> language of Claim 2 is or is not an "express limitation" of the Claim. Even assuming, arguendo, that the preamble to Claim 2 does expressly limit the claimed invention, the undisputed facts and methods underlying plaintiff's claimed-invention still remain the same: plaintiff's Nature paper explicitly described the role of certain RGD peptides in preventing kidney cells from attaching to a substrate which essentially shut down all cell growth or proliferation. The portion of the *'621 Patent* specification upon which Claim 2 relies describes a similar, if not identical, assay using the same peptide (GRGDSP) to detach the same type of cells (NRK cells) from an analogous substrate which, as it turns out, permanently keeps them from reattaching (or proliferating). *'621 Patent* at Col. 7, lines 18-34, 63-68. (*Integra Life Sciences I Ltd. v. Merck KGaA*, 1999 U.S. Dist. LEXIS 10380, *17, 50 USPQ2d 1846 (DC SCalif, 1999); emphasis added.)

In the present case, the reference of Bischoff, et al., teaches administration of mutant adenovirus to tumor cells that have lost RB gene function to effect killing of the $RB^{(-)}$ tumor cells. The method claims of the present method require direct administration of mutant adenovirus to endothelial cells and such administration is effective regardless of the RB-expression status of any associated tumor cells. That is, the reference of Bischoff, et al., does not explicitly describe the role of mutant adenovirus in selective killing of dividing endothelial cells independent of RB-expression status.

2.0.0 Conclusion

For the foregoing reasons, appellants respectfully submit that the Examiner has erred in rejecting claims 6, 7, 11, 15, 17 and 18 of this application. Specifically, the reference of Bischoff, et al, does not expressly or inherently teach all of the claimed elements of methods of the present invention, for example, as follows:

- The reference does not teach endothelial cells.
- The reference does not teach direct administration of a replication competent adenovirus, comprising a mutation in an E1A CR2 RB family member binding region, to endothelial cells.
- The reference does not teach preferential killing of dividing endothelial cells compared to quiescent endothelial cells by administration of such mutant adenovirus.
- The reference teaches only methods for specifically ablating $RB^{(-)}$ tumor cells by infecting $RB^{(-)}$ tumor cell populations with a E1A-$RB^{(-)}$ replication

defective adenovirus mutants; that is, the reference does not teach administration of such mutant adenovirus for preferential killing of dividing endothelial cells in cell populations without regard to RB-expression status of the cells in the population.

- The reference does not teach that such mutant adenovirus replicates to higher titers in the dividing endothelial cells versus wild-type adenovirus.
- The reference does not teach controlling angiogenesis in an animal by infection of dividing endothelial cells with such mutant adenovirus.

Appellants respectfully submit that the rejection of claims 6, 7, 11, 15, 17, and 18 under 35 U.S.C. §102(e) should be reversed. Accordingly, appellants respectfully request that the Board reverse the Examiner on all counts.

Respectfully submitted,

Date: 23 Feb 2008

By: Gary R Fabian

Gary R. Fabian, Ph.D.
Registration No. 33,875
Agent for Appellants

ONYX Pharmaceuticals, Inc.
2100 Powell Street
Emeryville, CA 94608
Phone: (510) 597-6502
Facsimile: (510) 597-6610.

CLAIMS APPENDIX

1. (Canceled)

2. (Canceled)

3. (Canceled)

4. (Canceled)

5. (Canceled)

6. (Rejected) The method of claim 11, wherein said mutation in the E1A-CR2 region is in Ad5 and comprises a deletion or substitution of one or more amino acids 122 through 129 encoded by said E1A-CR2 region.

7. (Rejected) The method of claim 11, wherein said mutation in the E1A-CR2 region is in Ad5 and comprises a deletion or substitution of one or more amino acids 111 through 123.

8. (Objected To) The method of claim 11, wherein said adenovirus is dl922/947.

9. (Objected To) The method of claim 11, wherein said adenovirus is dl1107.

10. (Objected To) The method of claim 11, wherein said adenovirus is pm928.

11. (Rejected) In a cell population comprising dividing and quiescent endothelial cells, a method for killing said dividing endothelial cells with substantially less killing of said quiescent endothelial cells, said method comprising contacting said cell population under infective conditions with a replication competent adenovirus, said adenovirus comprising a mutation in an E1A CR2 RB family member binding region of said adenovirus, and allowing sufficient time for said mutant adenovirus to infect said cell population, wherein said mutant adenovirus replicates to higher titers in said dividing cells than wild type adenovirus and said contacting is by direct administration of the replication competent adenovirus to the cell population.

12. (Canceled)

13. (Canceled)

14. (Canceled)

15. (Rejected) A method for controlling angiogenesis in an animal by substantially and selectively killing dividing microvascular endothelial cells compared to quiescent microvascular endothelial cells, said method comprising administering to said animal in need of said control a replication competent adenovirus comprising a mutation in an E1A-CR2 RB family member binding region of said adenovirus, and allowing sufficient time for said mutant adenovirus to infect said microvascular endothelial cells, wherein said administering is by direct administration of the replication competent adenovirus to the microvascular endothelial cells.

16. (Canceled)

17. (Rejected) The method of claim 15, wherein said mutation in the E1A-CR2 region is in Ad5 and comprises a deletion or substitution of one or more amino acids 122 through 129.

18. (Rejected) The method of claim 15, wherein said mutation in the E1A-CR2 region is in Ad5 and comprises a deletion or substitution of one or more amino acids 111 through 123.

19. (Objected To) The method of claim 15, wherein said adenovirus is dl922/947.

20. (Objected To) The method of claim 15, wherein said adenovirus is dl1107.

21. (Canceled)

22. (Canceled)

23. (Canceled)

24. (Canceled)

25. (Canceled)

26. (Allowed) A composition comprising a Rb binding site adenoviral mutant with a negative selection agent operably linked to a promoter, wherein said mutant is dl922/947.

27. (Allowed) A composition comprising a Rb binding site adenoviral mutant with a negative selection agent operably linked to a promoter, wherein said mutant is dl1107.

28. (Allowed) A composition comprising a Rb binding site adenoviral mutant with a negative selection agent operably linked to a promoter, wherein said mutant is pm928.

29. (Canceled)

30. (Canceled)

31. (Canceled)

32. (Canceled)

33. (Canceled)

34. (Objected To) The method of claim 15, wherein said adenovirus is pm928.

EVIDENCE APPENDIX

Appellants rely on the teachings of the specification as discussed herein above, as well as appellants' amendments to the claims and specification, including, the Response to Office Action, dated 15 March 2001, Response to Office Action, 17 July 2002, Response to Final Rejection and Amendment, filed 20 June 2005, Amendment and Response, dated 17 January 2006, Response to Office Action, dated 13 November 2006, and Amendment and Response to Final Office action, dated 27 September 2007.

Further, appellants rely on the references of Berse, B., et al., Molec. Cell. Biol. 1992 Feb;3(2):211-20, and Warren, R.S., et al., J. Clin. Invest. 1995 Apr;95(4):1789-97. Both of these references were submitted in the Information Disclosure Statement dated 13 November 2006, which is of record in the present application.

RELATED PROCEEDINGS APPENDIX

None.